Published in final edited form as:
Chemosens Percept. 2012 March 1; 5(1): 27–36. doi:10.1007/s12078-011-9112-6.

Correlation between Ventromedial Prefrontal Cortex Activation to Food Aromas and Cue-driven Eating: An fMRI Study

William J.A. Eiler II[1], **Mario Dzemidzic**[1,2], **K. Rose Case**[1], **Robert V. Considine**[3], and **David A. Kareken**[1,2,4]

[1]Department of Neurology, Indiana University School of Medicine, Indianapolis, Indiana, USA

[2]Department of Radiology, Indiana University School of Medicine, Indianapolis, Indiana, USA

[3]Division of Endocrinology, Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana, USA

[4]Department of Psychiatry, Indiana University School of Medicine, Indianapolis, Indiana, USA

Abstract

Food aromas are signals associated with both food's availability and pleasure. Previous research from this laboratory has shown that food aromas under fasting conditions evoke robust activation of medial prefrontal brain regions thought to reflect reward value (Bragulat, et al. 2010). In the current study, eighteen women (eleven normal-weight and seven obese) underwent a two-day imaging study (one after being fed, one while fasting). All were imaged on a 3T Siemens Trio-Tim scanner while sniffing two food (F; pasta and beef) odors, one non-food (NF; Douglas fir) odor, and an odorless control (CO). Prior to imaging, participants rated hunger and perceived odor qualities, and completed the Dutch Eating Behavior Questionnaire (DEBQ) to assess “Externality” (the extent to which eating is driven by external food cues). Across all participants, both food and non-food odors (compared to CO) elicited large blood oxygenation level dependent (BOLD) responses in olfactory and reward-related areas, including the medial prefrontal and anterior cingulate cortex, bilateral orbitofrontal cortex, and bilateral piriform cortex, amygdala, and hippocampus. However, food odors produced greater activation of medial prefrontal cortex, left lateral orbitofrontal cortex and inferior insula than non-food odors. Moreover, there was a significant correlation between the [F > CO] BOLD response in ventromedial prefrontal cortex and “Externality” sub-scale scores of the DEBQ, but only under the fed condition; no such correlation was present with the [NF > CO] response. This suggests that in those with high Externality, ventromedial prefrontal cortex may inappropriately valuate external food cues in the absence of internal hunger.

Keywords

Dutch Eating Behavior Questionnaire; Functional Magnetic Resonance Imaging; Obesity; Olfaction; Ventromedial Prefrontal Cortex

Corresponding Author: David A. Kareken, Ph.D., Department of Neurology, 541 Clinical Drive (CL 601), Indiana University School of Medicine, Indianapolis, IN 46202, Tel: 317 274-7327, Fax: 317 274-1337, dkareken@iupui.edu.

Financial Disclosures: The authors report no competing or conflicts of interest.

Introduction

Nearly a third of the US population meets the clinical criteria (Body Mass Index [BMI] > $30kg/m^2$) for obesity (Ogden et al., 2006), a condition that carries an increased risk of diabetes, cardiovascular disease, and certain cancers leading to increased morbidity and elevated health care costs (Flegal, 2005; Flegal et al., 1998). Despite a culture that demands ever larger portion sizes and relies on fast food franchises for the family dinner, not all individuals become obese. One factor that may confer an increased obesity risk is eating in response to external food cues, rather than internal hunger signals (Carnell & Wardle, 2008).

Neuroimaging techniques, such as functional magnetic resonance imaging (fMRI), provide a means to determine how obesity might be related to alterations in the brain's response to such external cues. Specifically, sensory stimuli that routinely accompany food ingestion (i.e. the sight, smell, and taste of food) acquire Pavlovian properties that can elicit both a motivational drive to eat (Berridge, 2007; Berridge et al., 2010), as well as initiate digestive processes (i.e., the “cephalic phase” of digestion) (Bellisle et al., 1985). Given the brain regions that support such motivational behavior, some have speculated about a significant overlap between obesity and drug addiction (Volkow & Wise, 2005). That is, sensory stimuli associated with these high reward value foods may trigger the same reward system activated in drug-seeking behavior, eliciting increased activation in known reward substrates such as the ventral striatum, amygdala, orbitofrontal cortex (OFC), medial prefrontal cortex (mPFC), hippocampus (Berthoud, 2006; Mela, 2006), and dorsolateral prefrontal cortex (Hare et al., 2009). Differential activation of these substrates may serve to draw attention to food sources, and govern behaviors involved in food-seeking and satiety.

Numerous studies have been conducted to evaluate neuronal activation following the presentation of visual food cues (i.e., photographs of appetizing foods). Rothemund and colleagues (Rothemund et al., 2007) observed increased neuronal activation within the dorsal striatum, anterior and posterior cingulate cortices and lateral OFC following the presentation of high-calorie food images, suggesting an increased role for brain areas associated with reward anticipation and motivation in obese women. A similar study in fasted women shown images of high-calorie foods reported increased activation in the medial and lateral OFC, as well as the mPFC, amygdala, anterior cingulate cortex (ACC), striatum and hippocampus (Stoeckel et al., 2008). Martin and colleagues also used food images to elicit activation prior to and following a standardized meal (Martin et al., 2010). This study demonstrated greater pre-meal activation of the mPFC and ACC within the obese individuals. Activation of the mPFC remained significantly higher in obese subjects compared to their normal weight counterparts following food intake, while the differences in ACC activation dissipated (Martin, et al., 2010). The above studies all show a strong role of the brain's reward system in the evaluation of visual food cues with greater activation typically observed in obese subjects.

While food images can be compelling, food aromas may be particularly effective cues given their prominent role in flavor perception (via retronasal olfaction), and thus their role in the sensory reinforcement that helps increase consumption (de Wijk et al., 2004; I. Fedoroff et al., 2003; I. C. Fedoroff et al., 1997; Jansen et al., 2003; Yeomans, 2006). Ventromedial and

medial prefrontal cortices are regions where neuronal activity varies as a function of the perceived reward value of stimuli (Hare, et al., 2009; Hare et al., 2008; Kable & Glimcher, 2007). Our laboratory has accordingly demonstrated that both alcoholic drink (Bragulat et al., 2008; Kareken et al., 2010a; Kareken et al., 2010b) and food aromas (Bragulat et al., 2010) robustly activate these medial frontal regions.

In the data that we report here from an ongoing study, we examine how maladaptive eating patterns may be related to medial prefrontal responses to food aromas in states of both hunger and satiety. In particular, we hypothesized that individuals who are high in "Externality", those with strong responses to external food cues (van Strien et al., 1986), would have stronger blood oxygenation level dependent (BOLD) responses to food odors in brain reward regions.

Materials and Methods

Participants

Eighteen women from the community participated, eleven of whom were normal-weight (BMI 22.2 ± 2.1, age 23.5 ± 4.4; mean ± Standard Deviation (SD)) and seven of whom were obese (BMI 36.3 ± 4.2, age 29.5 ± 6.0; Table 1). For the purposes of this study, the groups were collapsed and no BMI-based differences were examined. None of the participants had evidence of Axis-I psychiatric disorders or known disorders of the brain. All were non-smokers and performed within broad normal limits on a 20-item Smell Identification Test (Doty, 1995), with a range of 16 - 20 and a mean of 18.0. Individuals were excluded if they were pregnant or breast feeding within the past 6 months, had a history of diabetes or a fasting blood glucose level of 126mg/dl or greater. Individuals whose food preferences were inconsistent with the food aromas used or the meals provided were also excluded. All participants voluntarily signed informed consent statements approved by the institutional review board at Indiana University.

Procedures

All participants completed two non-contiguous study days: one "fasting day" when a lunch meal was withheld until after imaging, and one "fed day" when subjects ate a lunch meal to satiety before imaging. The order of the fasting and fed days was randomized, as was the lunch type (pasta with meat sauce or beef and noodles) consumed. On both study days, participants reported to the Indiana University Clinical Research Center (CRC) at approximately 6:30 am, whereupon weight and height were recorded, vital signs taken, and a urine screen for pregnancy and drug use was performed. At approximately 7:40 a.m. all participants consumed a standardized breakfast of turkey sausage, French toast (with margarine and syrup) and a fruit cup, with a choice of coffee, tea, diet soda, or water provided, per the subject's usual habit. The quantities of the breakfast were adjusted to provide 20% of the participant's daily caloric intake based on height, weight, age, and activity level.

Fasting Day—On fasting days, the participants remained in the CRC until ∼1:00 p.m., at which time they were escorted to the imaging suite, with lunch provided upon the subject's

return to the CRC immediately after imaging (∼ 3:00 – 4:00 p.m.). Lunches consisted of an *ad libitum* amount of the predetermined meal type (pasta or beef & noodles). Participants were provided 30 minutes in the CRC to finish their lunch meal before being released.

Fed Day—On fed days, participants remained in the CRC following breakfast until lunch was provided at 12:15 p.m.. Between breakfast and lunch participants could engage in normal activities (reading, watching television, computer use) except for sleeping. Lunches consisted of an *ad libitum* amount of the predetermined meal type (pasta or beef & noodles), with 30 minutes provided to finish lunch before leaving the CRC at 1:00 p.m. for imaging.

DEBQ—Subjects completed the Dutch Eating Behavior Questionnaire (DEBQ; Van Strien et al., 1986) on one of their two study days after breakfast and prior to imaging. The DEBQ consists of 33 items across three scales reflecting: Emotional (Psychosomatic) eating (eating in response to emotional distress), Externality (eating in response to external food cues, such as food sight and smell) and Restraint (over-eating in the wake of attempted restraint).

Olfactory Stimuli—All odorants were delivered at a constant rate of 2.0 l/min using a computer-controlled, eight-channel air-dilution olfactometer as previously described (Bragulat, et al., 2010; Bragulat, et al., 2008; Kareken et al., 2004). In this study, two classes of odorants (International Flavors & Fragrances, Union Beach, NJ) were presented to all participants: (i) food-related odors of pasta and roast beef; and (ii) a non-food, Douglas fir odor. Odorant concentrations were prepared by diluting the concentrated odorant in 1,2-propanediol (Sigma-Aldrich, St. Louis, MO). The pasta odorant was prepared to a 20% solution, the roast beef odorant to a 5% solution, and Douglas fir odorant was presented undiluted. A Porex® polyethylene disc (0.475″ dia. × 0.250″, Interstate Specialty Products, Sutton, MA) saturated with odorant was placed in the bottom of a glass vial, over which the olfactometer airstream was passed before being delivered to the participant via a small polytetrafluoroethylene tube.

Pre- and Post-MRI Hunger and Odorant Perception Assessment—Prior to entering the magnetic resonance imaging (MRI) scanner room, as well as following the imaging session, participants subjectively rated their hunger and the odorants' psychophysical characteristics. Participants smelled each odorant in a random order through the olfactometer while simultaneously viewing representative images on a computer monitor (e.g. pasta odorant presented with an appealing photograph of a plate of pasta with meat sauce). Immediately following each odorant, participants rated general hunger, as well as hunger specific to each of the food items, on a vertically oriented, 100 mm labeled magnitude scale (LMS) (Cardello et al., 2005), with “Greatest Imaginable Fullness” at the top, “Greatest Imaginable Hunger” on the bottom and “Neither Full nor Hungry” in the center (see Fig 1). Following hunger assessment, participants again sampled each odorant through the olfactometer in a random order and rated perceived intensity, pleasantness, and “representativeness” (the extent to which an odor smelled like its intended target). Odorant intensity was rated on Green's LMS modified to be horizontally oriented with “Barely Detectable” on the left-hand end and “Strongest Imaginable” on the right-hand end (Green et al., 1996). Odorant pleasantness and representativeness were assessed on visual analog

scales (VAS) of 1-9, with half point increments with “Very Unpleasant” and “Not at all Representative” on the left-hand end and “Very Pleasant” and “Very Representative” on the right-hand end, respectively. Odorant perception prior to fMRI session was reassessed until each odorant was perceived by the participant as being within 2 intensity increments of the other odorants' perceived intensity, with adjustments in the air-dilution of the odorant made between each assessment (generally this required ∼2 adjustments).

Intra-MRI Hunger Assessment—Subjective hunger was assessed at three time points during imaging; 1) prior to the first functional scan, 2) following the second functional scan and 3) again after the fourth (last) functional scan. As above, the participant was asked to rate their hunger in general, as well as their hunger specifically for pasta and beef and noodles on the same VAS presented outside the MRI. However, these intra-MRI assessments were not preceded by odorant presentation.

Activation Paradigm—Participants underwent four functional imaging scans of olfactory stimulation, with each odorant presented 6 times per scan in a mixed-event design that also included 6 presentations of the odorless control, for a total of 24 presentations per event type. Four distinct sequences of event presentations were generated by OptSeq2 (http://surfer.nmr.mgh.harvard.edu/optseq/) resulting in 8-18 sec inter-stimulus intervals within 6:27 min long scans. Each sequence was run once per MRI session in a randomized order. To evaluate compliance, participants were prompted (via a 750 ms long, 750 Hz tone) to report an odorant's presence (left button) or absence (right button) on a MRI compatible HHSC-TRK-1 trackball (Current Designs, Philadelphia, PA).

Image Acquisition

Imaging was performed on a Siemens (Erlangen, Germany) 3T Magnetom Trio-Tim scanner with a 12-channel head coil array. To facilitate anatomic localization of the functional data, a high resolution anatomic image was acquired using a 3D magnetization prepared rapid gradient echo (MPRAGE) MRI sequence (160 sagittal slices, 1.0×1.0×1.2 mm^3 voxels, field of view (FOV) 256 × 256 mm, repetition time (TR) 2300 ms, echo time (TE) 2.91 ms, flip angle (FA) 9°, duration 9:14). BOLD-sensitive volumes were acquired with an echo-planar imaging pulse sequence (gradient echo, TR 2250 ms, TE 29 ms, FA 78°, FOV 220×220 mm, 39 interleaved 3-mm thick slices, 2.5×2.5×3.0 mm^3 voxels, generalized auto-calibrating partially parallel acquisition (GRAPPA) factor of 2). Three-dimensional prospective acquisition correction (3D-PACE) algorithm (Thesen et al., 2000) was enabled to adjust image acquisition in real time, accounting for head movement and significantly reducing motion-related artifacts. In addition, a deformable foam cushion stabilized head position. Participants were instructed to keep their eyes closed for the duration of each functional scan.

Image Processing and Analysis

Imaging data were preprocessed using standard SPM8 (Welcome Department of Imaging Neuroscience, University College, London, UK) procedures (slice-time acquisition correction, realignment, co-registration, and segmentation/normalization) after verification for artifacts and excessive motion. Each subject's MPRAGE image was segmented into

tissue classes and parameters of this non-linear transformation were utilized to convert participant's structural MRI and realigned, co-registered functional image volumes into the Montreal Neurological Institute (MNI) stereotactic space. The resulting normalized functional image volumes were interpolated to 2 mm per side isotropic voxels and smoothed by a 6 mm full-width at half-maximum isotropic Gaussian kernel.

Responses to discrete, 2-sec periods of odorant (or sham) valve events in the post-processed image time series were convolved with a standard hemodynamic response function and its time and dispersion derivatives in a within-subject “first-level” analysis. The six movement parameters from realignment were included as regressors to account for residual movement-induced effects. A high-pass filter with a cut-off of 1/128 Hz was applied to each voxel's time series to remove low frequency noise. This model estimated within-subject activation effects, with each Food (F) or Non-Food (NF) odorant set contrasted against sniffing of an odorless control event (CO; i.e., sham valve opening that shunted the same air source without odorant delivery) resulting in the following BOLD response contrasts: [F > CO] and [NF > CO], respectively. The comparison of Food to Non-Food odors also included the odorless sniffing baseline (i.e., [F > NF] = [F > CO] > [NF > CO]). The MarsBar toolbox (Brett et al., 2002) was used to define functional regions of interest (ROI), and to extract mean contrast values (activation) for each of the participants for the purposes of plotting activation as a function of Externality.

Results

Odor perception and hunger

Odor ratings—No significant group differences in odor perception were observed between normal-weight and obese participants ($p > 0.05$); therefore, all perception data were collapsed across groups. All eighteen participants perceived the intensity of the pasta (16.6 ± 9.8), roast beef (17.3 ± 9.6), and Douglas fir (17.5 ± 9.8) odors to be similar. Participants also found the odors to be insignificantly different in pleasantness (pasta 7.0 ± 1.0; roast beef 7.2 ± 0.9; Douglas fir 7.0 ± 1.5) and representativeness (pasta 7.5 ± 1.1, roast beef 8.1 ± 0.5 and Douglas fir 8.1 ± 0.7).

Hunger ratings—Hunger ratings were insignificantly different as a function of either BMI group ($p > 0.10$) or the type of odor present when making hunger ratings ($p > 0.30$). Therefore, hunger score data were collapsed across groups and all food odors for session analyses. Across all subjects, marked between-session differences in assessed hunger emerged for hunger in general, as well as for expressed hunger for a given food (pasta and roast beef, after smelling each), with significantly ($p < 0.001$) greater hunger in the Fast session than the Fed session (Figure 1).

Food consumption—Participants consumed an average of 592.3 grams of food with no significant difference in consumption between lean and obese participants ($p = 0.47$) and no significant difference in food consumed between fed (eating at a standard lunch time) and fasting days (eating 3-4 hours after missing lunch; $p = 0.40$).

BOLD activation

BOLD activation of F compared to NF—In this sample, brain activation did not differ as a function of either BMI group or session, assessed either from individual odor classes, or as a difference between odor classes. Pooled over both sessions, both food and non-food odors elicited significant activation in a number of limbic and reward-related areas (Table 2, Figure 2 A, B). These areas included medial prefrontal cortex (mPFC) and the ACC. Areas receiving olfactory bulb projections (piriform cortex, amygdala) also showed a prominent BOLD response, as did the hippocampus. When contrasted against non-food odors, food odors produced greater activation in medial prefrontal cortex (Figure 2 C; peak $p = 0.001$, at [−4, 40, 2]), and in left lateral orbital cortex, extending into the inferior insula (Figure 2 D; peak $p = 0.001$ at [−40, 20, −18]).

DEBQ and correlations—The sample's mean DEBQ score was 55.3 ± 17.3, with no significant difference observed between the normal-weight and obese participants ($p = 0.09$). Mean scores on the Restraint (21.4 ± 1.2) and Externality (18.9 ± 2.7) sub-scales were not different between groups (ps > 0.53), although a significant group difference was present in the Psychosomatic sub-scale (obese = 25.0 ± 3.3, normal-weight = 15.0 ± 2.8; $t[16] = 2.30$, $p = 0.04$).

Correlations between food odor-induced activation and the scores on the Externality subscale of the DEBQ were examined. Of particular interest were correlations with the [F > CO] BOLD contrast under both Fed and Fast conditions. The [F > CO] response correlated with Externality only under the Fed condition (Figure 3 B), and in the ventral aspect of the mPFC cluster (vmPFC) activated by food odors (i.e., under the [F >CO] contrast in the Fed condition; Figure 3 A). To illustrate the distribution of the effects, we extracted mean [F > CO] contrast values from the vmPFC cluster of significant correlation, as well as the contrast values from the same region in the [NF > CO] contrast. The positive correlation between [F > CO] and Externality observed in the Fed session (Figure 4 A) was absent in the Fast session (Figure 4 B). There were no significant voxel-wise correlations between [NF > CO] and Externality under either the Fed or Fast sessions (p's > 0.05; Figure 4 C, D), and no significant voxel-wise correlations between either [F > CO] or [NF > CO] in other activating reward areas. Adding BMI as a covariate did not change the results.

Discussion

As olfaction is a primary foraging mechanism across nearly all species, the aromas of ingested primary rewards should be particularly salient reward cues. Moreover, food aromas are routinely present during consumption and critical to flavor perception through the means of retronasal olfaction (Mozell et al., 1969; Murphy et al., 1977; Shepherd, 2006). Thus, via Pavlovian conditioning, they become closely associated with food availability, foods' inherently pleasurable sensations, and the rewarding sensations (or negative reinforcement) from hunger relief and satiety. In the present study, both food and non-food aromas led to BOLD activation in a number of brain regions associated with both reward and olfaction. Medial frontal cortex (including some ACC) activation was, however, largest to food odors. The location of this BOLD response is consistent with others' observations of regional

activation that correlates with the perceived value of a reward (Bray et al., 2010; Hare, et al., 2009; Hare et al., 2011; Hare, et al., 2008; Kable & Glimcher, 2007). The OFC, also known to play a role in coding appetitive goal values (Arana et al., 2003; Chib et al., 2009; Hare et al., 2010; Hare, et al., 2008; Paulus & Frank, 2003; Plassmann et al., 2010), similarly showed a significant BOLD response to food odors above and beyond that of non-food odors in a location previously reported to display increased activity in obese participants following the presentation of high-calorie, food images (Stoeckel et. al., 2008). Although normally studied in the context of anterograde learning and memory, the hippocampus has been shown to regulate food intake (Davidson et al., 2007; Tracy et al., 2001), distinguish between introceptive signals of hunger and satiety (Hebben et al., 1985) (Davidson & Jarrard, 1993; Hock & Bunsey, 1998), and activate in the presence of food related stimuli and food cravings (Bragulat, et al., 2010; Cornier et al., 2009; Gautier et al., 1999; LaBar et al., 2001; Pelchat et al., 2004). Although the hippocampus did activate to food odors in our study, the activation was not significantly different from that of non-food odors, at least in this mixed sample.

Medial frontal cortex has become a compelling target in the study of stimuli that are either rewarding in and of themselves (such as the secondary reinforcer of money; e.g., (Kable & Glimcher, 2007)), or sensory stimuli that are classically conditioned with drug rewards, such as alcohol intoxication (Bragulat, et al., 2008; Filbey et al., 2008; Kareken, et al., 2010a,b; Kareken et al., 2011; Myrick et al., 2008). In particular, activation in this region appears to correlate with the extent of the reward's perceived value and with decision-making based on these valuations (Chib, et al., 2009; Hare, et al., 2010; Hare, et al., 2009; Hare, et al., 2011; Noonan et al., 2011). Most recently, Noonan and colleagues (2011) have shown that the mPFC specifically represents the value of anticipated outcomes. Similar work by Hare and colleagues suggests that mPFC activation drives choice when confronted with salient stimuli related to food reward (Hare, et al., 2009; Hare, et al., 2011). In our own hands, we have observed remarkably similar medial prefrontal activation from not only food aromas (Bragulat, et al., 2010), but also the aromas of preferred alcoholic drinks (Bragulat, et al., 2008)— activation which varies as a function of particular alcoholism risk factors, such as familial alcoholism and polymorphisms in the *GABRA2* gene (Kareken, et al., 2010a; Kareken, et al., 2010b). Given the previously documented relationship between the mPFC response to stimuli associated with reward and perceived reward value, one might expect a significant relationship between the extent to which feeding is driven by external cues (i.e., the extent to which food cues can induce a motivated state) and food cue induced activity in this region. Consistent with this notion, we did, indeed, note a region of ventral mPFC that not only responded to food odors, but also correlated with the degree to which subjects reported themselves to be high in “Externality” on the DEBQ scale, although this appeared only in the post-meal, Fed condition. Activation from non-food odors under both Fed and Fast sessions was not significantly correlated with Externality scores.

The DEBQ Externality sub-scale was designed to measure the phenomenon of “external eating”, defined as eating in response to food related stimuli irrespective of internal signals of hunger or satiety (Schachter et al., 1968; van Strien, et al., 1986). Those scoring high on the Externality sub-scale need not be obese, as individuals are endowed with their own range

of homeostatically regulated body weight (Herman & Polivy, 1980; Polivy & Herman, 1983). This is true for our dataset, which shows no significant group difference in Externality scores, although it is conceivable that with larger samples our small difference ($p = 0.09$) will become significant. The fact that a correlation emerged solely under the Fed condition may not be particularly surprising, as irrespective of Externality, most individuals should have a significant response to food stimuli while hungry (Castellanos et al., 2009). The strong positive correlation under the Fed condition between Externality and the food odor activation suggests that when sated, vmPFC in these individuals may continue to signal continued rewarding value that is disproportionate to recent food intake. In fact, the peak voxel effect at [−4, 34, −14] in our correlation between Externality and the [F > CO]response was very close to a focus [−6, 41, −14] in the most recent study conducted by Hare, et al. (2011) in which mPFC activation from food images correlated with taste and health ratings of the images. Thus, we postulate that individuals high in Externality may overeat, regardless of hunger, in part from inappropriate food valuation signals in the mPFC — a supposition supported by work from Gearhardt et al. (2011), in which medial OFC BOLD responses to milkshake tastes correlate positively with Yale Food Addiction Scale scores.

Although some between-group trends between normal-weight and obese subjects did begin to emerge in the data reported here, none reached statistical significance. Thus, while the activations in similar studies were all greater in obese subjects when compared to normal weight controls, the lack of a group difference in our ongoing study is very likely due to the sample sizes. In addition, pooling over obese and normal-weight participants may also explain why we observed no differences in [F > CO] activation between Fed and Fasting states, especially over the relatively short normal-meal fasting interval between breakfast and lunch. It should also be noted that the normal-weight group participants are younger than the obese participants (23.6 ± 4.4 and 30.1 ± 5.0 respectively, $p < 0.05$). To date, we have also not seen sensory-specific satiety effects, such as those reported by O'Doherty and colleagues (2000), where activation to a food odor is reduced after the food it represents is eaten to satiety. However, a larger sample may again help determine whether such an effect exists in these subjects.

Conclusions

In summary, this study demonstrated that the peak differences between food and nonfood odors arise within medial prefrontal and lateral orbitofrontal areas. The current study also revealed a positive correlation between ventral mPFC activation from food aromas and scores on the Externality sub-scale of the DEBQ under sated conditions. This suggests the possibility that, in subjects whose feeding behaviors are driven strongly by external cues, the mPFC may be involved in the inappropriate valuation of external food stimuli, even after diminished hunger.

Acknowledgments

Supported by the National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases to RVC and DAK (R01 DK089070) and the Indiana CTSI, Indiana Clinical Research Center, UL RR025761. Special thanks to MR technologists Michele Beal and Courtney Robbins. We also thank Richard Mattes, MPH, Ph.D.,

R.D., (Purdue University) for his advice and assistance; Cheryl Armstrong, Ph.D., M.B.A., R.D. for her help with meal planning, preparation and caloric intake measures; Stephen Warrenburg, Ph.D., at International Flavors & Fragrances for their donation of the odorant stimuli; and Kieren Mather, M.D. for his medical support.

References

Arana FS, Parkinson JA, Hinton E, Holland AJ, Owen AM, Roberts AC. Dissociable contributions of the human amygdala and orbitofrontal cortex to incentive motivation and goal selection. J Neurosci. 2003; 23(29):9632–9638. [PubMed: 14573543]

Bellisle F, Louis-Sylvestre J, Demozay F, Blazy D, Le Magnen J. Cephalic phase of insulin secretion and food stimulation in humans: a new perspective. Am J Physiol. 1985; 249(6 Pt 1):E639–645. [PubMed: 3909830]

Berridge KC. The debate over dopamine's role in reward: the case for incentive salience. Psychopharmacology (Berl). 2007; 191(3):391–431. [PubMed: 17072591]

Berridge KC, Ho CY, Richard JM, DiFeliceantonio AG. The tempted brain eats: pleasure and desire circuits in obesity and eating disorders. Brain Res. 2010; 1350:43–64. [PubMed: 20388498]

Berthoud HR. Homeostatic and non-homeostatic pathways involved in the control of food intake and energy balance. Obesity (Silver Spring). 2006; 14 Suppl 5:197S–200S. [PubMed: 17021366]

Bragulat V, Dzemidzic M, Bruno C, Cox CA, Talavage T, Considine RV, Kareken DA. Food-related odor probes of brain reward circuits during hunger: a pilot FMRI study. Obesity (Silver Spring). 2010; 18(8):1566–1571. [PubMed: 20339365]

Bragulat V, Dzemidzic M, Talavage T, Davidson D, O'Connor SJ, Kareken DA. Alcohol sensitizes cerebral responses to the odors of alcoholic drinks: an fMRI study. Alcohol Clin Exp Res. 2008; 32(7):1124–1134. [PubMed: 18540915]

Bray S, Shimojo S, O'Doherty JP. Human medial orbitofrontal cortex is recruited during experience of imagined and real rewards. J Neurophysiol. 2010; 103(5):2506–2512. [PubMed: 20200121]

Brett, M.; Anton, J.; Valabregue, R.; Poline, J. Region of interest analysis using an SPM toolbox. Paper presented at the 8th International Conference on Functional Mapping of the Human Brain; Sendai, Japan. 2002.

Cardello AV, Schutz HG, Lesher LL, Merrill E. Development and testing of a labeled magnitude scale of perceived satiety. Appetite. 2005; 44(1):1–13. [PubMed: 15604029]

Carnell S, Wardle J. Appetite and adiposity in children: evidence for a behavioral susceptibility theory of obesity. Am J Clin Nutr. 2008; 88(1):22–29. [PubMed: 18614720]

Castellanos EH, Charboneau E, Dietrich MS, Park S, Bradley BP, Mogg K, Cowan RL. Obese adults have visual attention bias for food cue images: evidence for altered reward system function. Int J Obes (Lond). 2009; 33(9):1063–1073. [PubMed: 19621020]

Chib VS, Rangel A, Shimojo S, O'Doherty JP. Evidence for a common representation of decision values for dissimilar goods in human ventromedial prefrontal cortex. J Neurosci. 2009; 29(39): 12315–12320. [PubMed: 19793990]

Cornier MA, Salzberg AK, Endly DC, Bessesen DH, Rojas DC, Tregellas JR. The effects of overfeeding on the neuronal response to visual food cues in thin and reduced-obese individuals. PLoS One. 2009; 4(7):e6310. [PubMed: 19636426]

Davidson TL, Jarrard LE. A role for hippocampus in the utilization of hunger signals. Behav Neural Biol. 1993; 59(2):167–171. [PubMed: 8476385]

Davidson TL, Kanoski SE, Schier LA, Clegg DJ, Benoit SC. A potential role for the hippocampus in energy intake and body weight regulation. Curr Opin Pharmacol. 2007; 7(6):613–616. [PubMed: 18032108]

de Wijk RA, Polet IA, Engelen L, van Doorn RM, Prinz JF. Amount of ingested custard dessert as affected by its color, odor, and texture. Physiol Behav. 2004; 82(2-3):397–403. [PubMed: 15276804]

Doty, RL. Sensonics. 3rd. 1995. The Smell Identification TestTM: Administration Manual.

Fedoroff I, Polivy J, Herman CP. The specificity of restrained versus unrestrained eaters' responses to food cues: general desire to eat, or craving for the cued food? Appetite. 2003; 41(1):7–13. [PubMed: 12880616]

Fedoroff IC, Polivy J, Herman CP. The effect of pre-exposure to food cues on the eating behavior of restrained and unrestrained eaters. Appetite. 1997; 28(1):33–47. [PubMed: 9134093]

Filbey FM, Claus E, Audette AR, Niculescu M, Banich MT, Tanabe J, et al. Hutchison KE. Exposure to the taste of alcohol elicits activation of the mesocorticolimbic neurocircuitry. Neuropsychopharmacology. 2008; 33(6):1391–1401. [PubMed: 17653109]

Flegal KM. Epidemiologic aspects of overweight and obesity in the United States. Physiol Behav. 2005; 86(5):599–602. [PubMed: 16242735]

Flegal KM, Carroll MD, Kuczmarski RJ, Johnson CL. Overweight and obesity in the United States: prevalence and trends, 1960-1994. Int J Obes Relat Metab Disord. 1998; 22(1):39–47. [PubMed: 9481598]

Gautier JF, Chen K, Uecker A, Bandy D, Frost J, Salbe AD, et al. Tataranni PA. Regions of the human brain affected during a liquid-meal taste perception in the fasting state: a positron emission tomography study. Am J Clin Nutr. 1999; 70(5):806–810. [PubMed: 10539739]

Gearhardt AN, Yokum S, Orr PT, Stice E, Corbin WR, Brownell KD. Neural correlates of food addiction. Arch Gen Psychiatry. 2011; 68(8):808–816. [PubMed: 21464344]

Green BG, Dalton P, Cowart B, Shaffer G, Rankin K, Higgins J. Evaluating the 'Labeled Magnitude Scale' for measuring sensations of taste and smell. Chem Senses. 1996; 21(3):323–334. [PubMed: 8670711]

Hare TA, Camerer CF, Knoepfle DT, Rangel A. Value computations in ventral medial prefrontal cortex during charitable decision making incorporate input from regions involved in social cognition. J Neurosci. 2010; 30(2):583–590. [PubMed: 20071521]

Hare TA, Camerer CF, Rangel A. Self-control in decision-making involves modulation of the vmPFC valuation system. Science. 2009; 324(5927):646–648. [PubMed: 19407204]

Hare TA, Malmaud J, Rangel A. Focusing attention on the health aspects of foods changes value signals in vmPFC and improves dietary choice. J Neurosci. 2011; 31(30):11077–11087. [PubMed: 21795556]

Hare TA, O'Doherty J, Camerer CF, Schultz W, Rangel A. Dissociating the role of the orbitofrontal cortex and the striatum in the computation of goal values and prediction errors. J Neurosci. 2008; 28(22):5623–5630. [PubMed: 18509023]

Hebben N, Corkin S, Eichenbaum H, Shedlack K. Diminished ability to interpret and report internal states after bilateral medial temporal resection: case H.M. Behav Neurosci. 1985; 99(6):1031–1039. [PubMed: 3843537]

Herman, CP.; Polivy, J. Restrained eating. In: Stunkard, AJ., editor. Obesity. Philadelphia, London, Toronto: Saunders; 1980. p. 208-225.

Hock BJ Jr, Bunsey MD. Differential effects of dorsal and ventral hippocampal lesions. J Neurosci. 1998; 18(17):7027–7032. [PubMed: 9712671]

Jansen A, Theunissen N, Slechten K, Nederkoorn C, Boon B, Mulkens S, Roefs A. Overweight children overeat after exposure to food cues. Eat Behav. 2003; 4(2):197–209. [PubMed: 15000982]

Kable JW, Glimcher PW. The neural correlates of subjective value during intertemporal choice. Nat Neurosci. 2007; 10(12):1625–1633. [PubMed: 17982449]

Kareken DA, Bragulat V, Dzemidzic M, Cox C, Talavage T, Davidson D, O'Connor SJ. Family history of alcoholism mediates the frontal response to alcoholic drink odors and alcohol in at-risk drinkers. Neuroimage. 2010a; 50(1):267–276. [PubMed: 20004725]

Kareken DA, Claus ED, Sabri M, Dzemidzic M, Kosobud AE, Radnovich AJ, et al. Li TK. Alcohol-related olfactory cues activate the nucleus accumbens and ventral tegmental area in high-risk drinkers: preliminary findings. Alcohol Clin Exp Res. 2004; 28(4):550–557. [PubMed: 15100605]

Kareken DA, Grahame N, Dzemidzic M, Walker MJ, Lehigh CA, O'Connor SJ. fMRI of the brain's response to stimuli experimentally paired with alcohol intoxication. Psychopharmacology (Berl). 2011

Kareken DA, Liang T, Wetherill L, Dzemidzic M, Bragulat V, Cox C, et al. Foroud T. A polymorphism in GABRA2 is associated with the medial frontal response to alcohol cues in an fMRI study. Alcohol Clin Exp Res. 2010b; 34(12):2169–2178. [PubMed: 20698837]

LaBar KS, Gitelman DR, Parrish TB, Kim YH, Nobre AC, Mesulam MM. Hunger selectively modulates corticolimbic activation to food stimuli in humans. Behav Neurosci. 2001; 115(2):493–500. [PubMed: 11345973]

Martin LE, Holsen LM, Chambers RJ, Bruce AS, Brooks WM, Zarcone JR, et al. Savage CR. Neural mechanisms associated with food motivation in obese and healthy weight adults. Obesity (Silver Spring). 2010; 18(2):254–260. [PubMed: 19629052]

Mela DJ. Novel food technologies: enhancing appetite control in liquid meal replacers. Obesity (Silver Spring). 2006; 14 Suppl 4:179S–181S. [PubMed: 16931503]

Mozell MM, Smith BP, Smith PE, Sullivan RL Jr, Swender P. Nasal chemoreception in flavor identification. Arch Otolaryngol. 1969; 90(3):367–373. [PubMed: 5803671]

Murphy C, Cain WS, Bartoshuk LM. Mutual action of taste and olfaction. Sens Processes. 1977; 1(3): 204–211. [PubMed: 887950]

Myrick H, Anton RF, Li X, Henderson S, Randall PK, Voronin K. Effect of naltrexone and ondansetron on alcohol cue-induced activation of the ventral striatum in alcohol-dependent people. Arch Gen Psychiatry. 2008; 65(4):466–475. [PubMed: 18391135]

Noonan MP, Mars RB, Rushworth MF. Distinct roles of three frontal cortical areas in reward-guided behavior. J Neurosci. 2011; 31(40):14399–14412. [PubMed: 21976525]

Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999-2004. JAMA. 2006; 295(13):1549–1555. [PubMed: 16595758]

Paulus MP, Frank LR. Ventromedial prefrontal cortex activation is critical for preference judgments. Neuroreport. 2003; 14(10):1311–1315. [PubMed: 12876463]

Pelchat ML, Johnson A, Chan R, Valdez J, Ragland JD. Images of desire: food-craving activation during fMRI. Neuroimage. 2004; 23(4):1486–1493. [PubMed: 15589112]

Plassmann H, O'Doherty JP, Rangel A. Appetitive and aversive goal values are encoded in the medial orbitofrontal cortex at the time of decision making. J Neurosci. 2010; 30(32):10799–10808. [PubMed: 20702709]

Polivy, J.; Herman, CP. Breaking the Diet Habit: The Natural Weight Alternative. New York: Basic Books; 1983.

Rothemund Y, Preuschhof C, Bohner G, Bauknecht HC, Klingebiel R, Flor H, Klapp BF. Differential activation of the dorsal striatum by high-calorie visual food stimuli in obese individuals. Neuroimage. 2007; 37(2):410–421. [PubMed: 17566768]

Schachter S, Goldman R, Gordon A. Effects of fear, food deprivation, and obesity on eating. J Pers Soc Psychol. 1968; 10(2):91–97. [PubMed: 5725907]

Shepherd GM. Smell images and the flavour system in the human brain. Nature. 2006; 444(7117): 316–321. [PubMed: 17108956]

Stoeckel LE, Weller RE, Cook EW 3rd, Twieg DB, Knowlton RC, Cox JE. Widespread reward-system activation in obese women in response to pictures of high-calorie foods. Neuroimage. 2008; 41(2): 636–647. [PubMed: 18413289]

Thesen S, Heid O, Mueller E, Schad LR. Prospective acquisition correction for head motion with image-based tracking for real-time fMRI. Magn Reson Med. 2000; 44(3):457–465. [PubMed: 10975899]

Tracy AL, Jarrard LE, Davidson TL. The hippocampus and motivation revisited: appetite and activity. Behav Brain Res. 2001; 127(1-2):13–23. [PubMed: 11718882]

van Strien T, Frijters JE, Bergers GP, Defares PB. Dutch eating behavior questionnaire for assessment of restrained, emotional and external eating behaviour. International Journal of Eating Disorders. 1986; 5(2):21.

Volkow ND, Wise RA. How can drug addiction help us understand obesity? Nat Neurosci. 2005; 8(5): 555–560. [PubMed: 15856062]

Yeomans MR. Olfactory influences on appetite and satiety in humans. Physiol Behav. 2006; 87(4): 800–804. [PubMed: 16545846]

Abbreviations

3D-PACE	Three-Dimensional Prospective Acquisition Correction
ACC	Anterior Cingulate Cortex
BMI	Body Mass Index
BOLD	Blood Oxygenation Level Dependent
CO	Control, Odorless Sniffing
CRC	Clinical Research Center
DEBQ	Dutch Eating Behavior Questionnaire
F	Food Odors
FA	Flip Angle
FDR	False Discovery Rate
fMRI	Functional Magnetic Resonance Imaging
FOV	Field of View
GRAPPA	Generalized Auto-Calibrating Partially Parallel Acquisition
LMS	Labeled Magnitude Scale
MNI	Montreal Neurological Institute
mPFC	Medial Prefrontal Cortex
MPRAGE	Magnetization Prepared Rapid Gradient Echo
MRI	Magnetic Resonance Imaging
NF	Non-Food Odor
OFC	Orbitofrontal Cortex
ROI	Region of Interest
SD	Standard Deviation
TR	Repetition Time
TE	Echo Time
VAS	Visual Analog Scale
vmPFC	Ventromedial Prefrontal Cortex

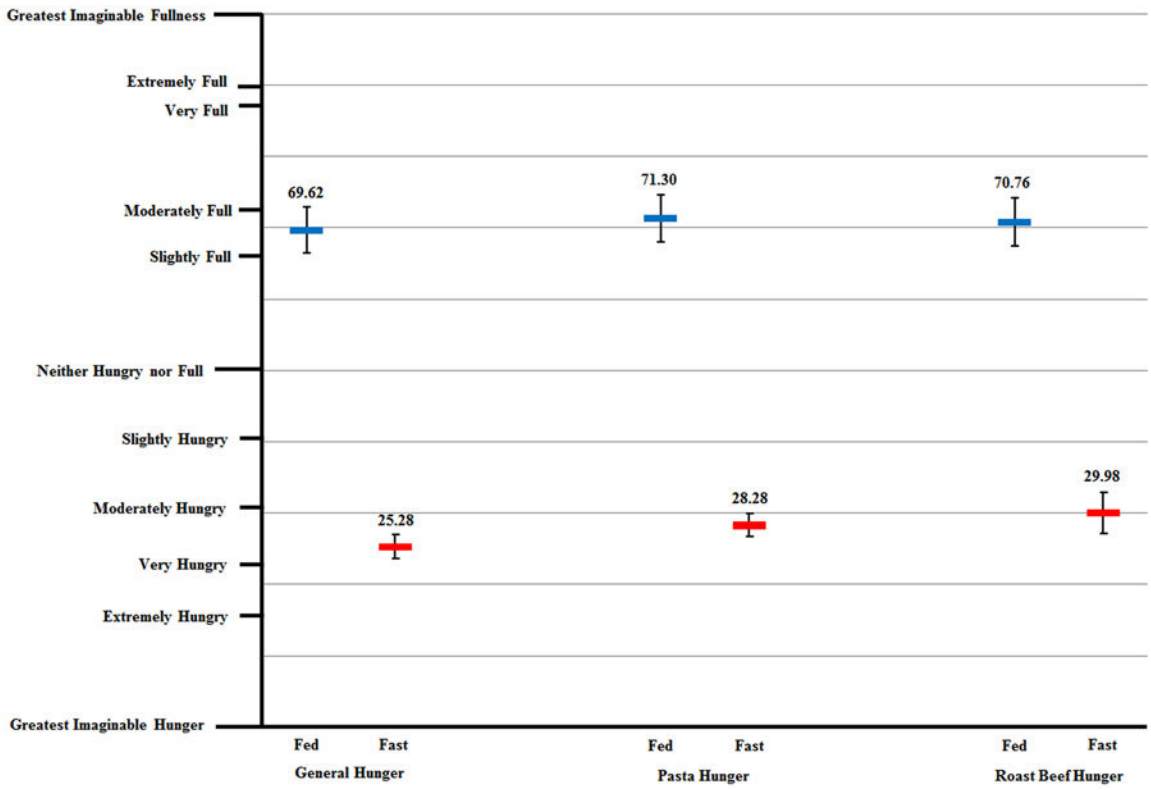

Figure 1.

Mean hunger scores for hunger type (General, Pasta and Roast Beef) assessed by Cardello's LMS (Cardello, et al., 2005) under both the Fed (*blue bars*) and Fast (*red bars*) session. The y-axis values indicate the labeled magnitude scale (100 mm in length) presented to the participants when rating hunger. All between-session comparisons resulted in significant ($p < 0.001$) differences with greater hunger experienced in the Fast session than the Fed session.

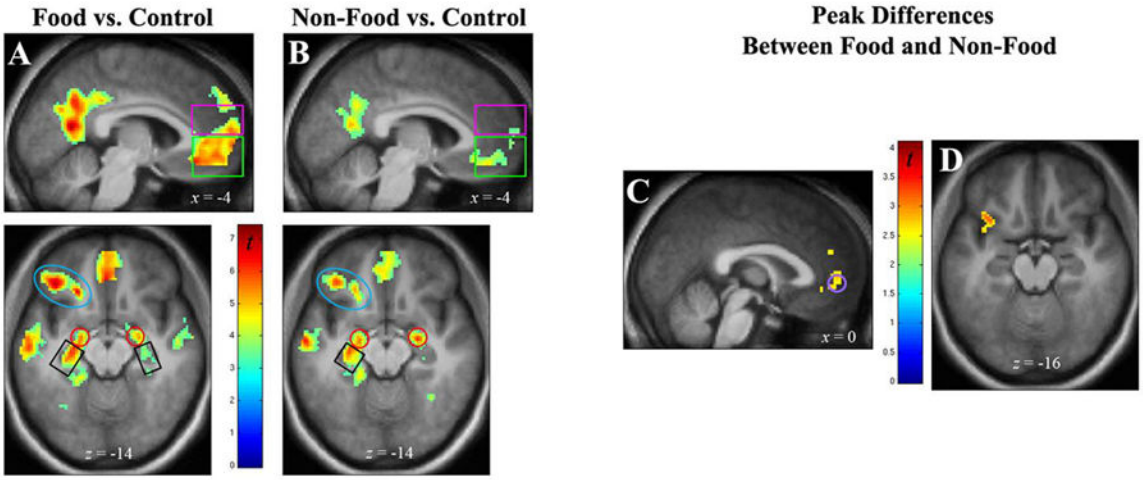

Figure 2.

BOLD activation induced by sniffing odors in a mixed sample of 18 obese and normal-weight women under both Fed and Fast sessions. **A)** Food (F) odors compared to sniffing odorless control events (CO); [F > CO] contrast. **B)** Non-Food (NF) odors compared to CO; [NF > CO] contrast. **C and D)** Direct comparison of Food and Non-Food odors; [F > NF] contrast. **A - D:** magenta box, medial prefrontal cortex; green box, ventromedial prefrontal cortex; blue ovals, left lateral orbitofrontal cortex; red circles, left and right amydala; black boxes, left and right hippocampus; purple circle, 6mm sphere encompassing peak of significant medial prefrontal activation reported in (Bragulat et al., 2010). Results in panels **A** and **B** displayed at cluster-level significance, q_{clust}(FWE) < 0.005, voxel-wise height threshold, $p < 0.001$ (uncorrected). Results in panels C and D displayed at $p < 0.01$ (uncorrected), cluster size, $k > 25$. Color bar indicates t statistic values.

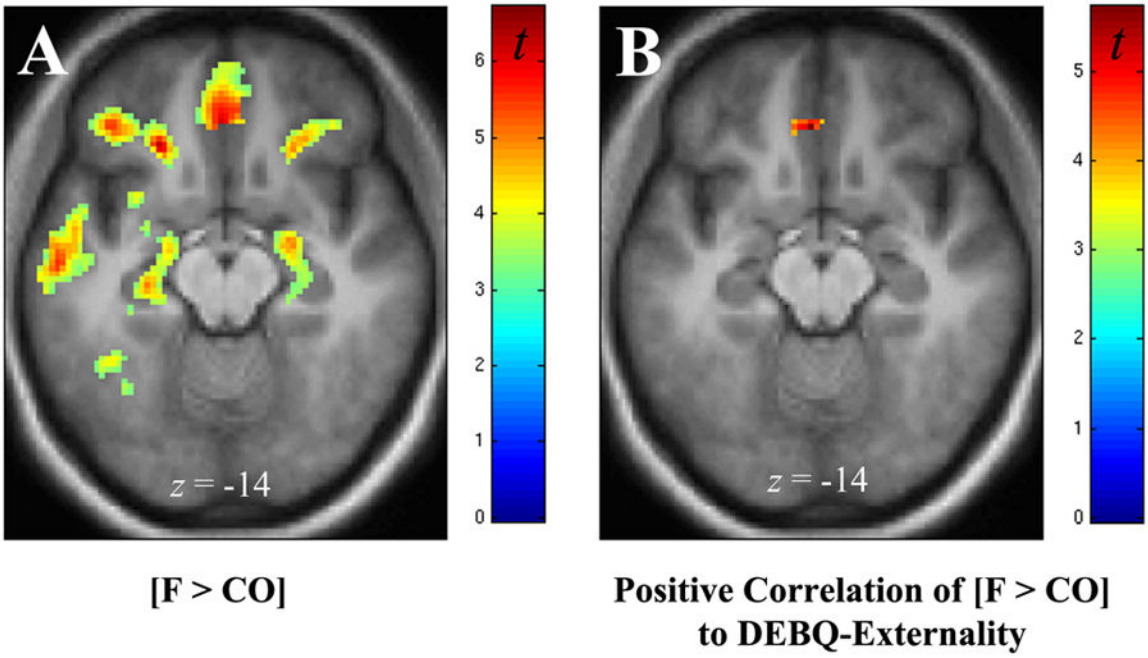

Figure 3.

A) [F > CO] BOLD contrast in a mixed sample of 18 obese and normal-weight women under the Fed session. Voxel-wise height threshold, $p < 0.001$ (uncorrected), cluster size, $k > 50$. **B)** Positive correlation between DEBQ externality sub-scale scores and [F > CO] response under the Fed session. Display threshold, $p < 0.001$ (uncorrected), cluster size, $k > 10$.

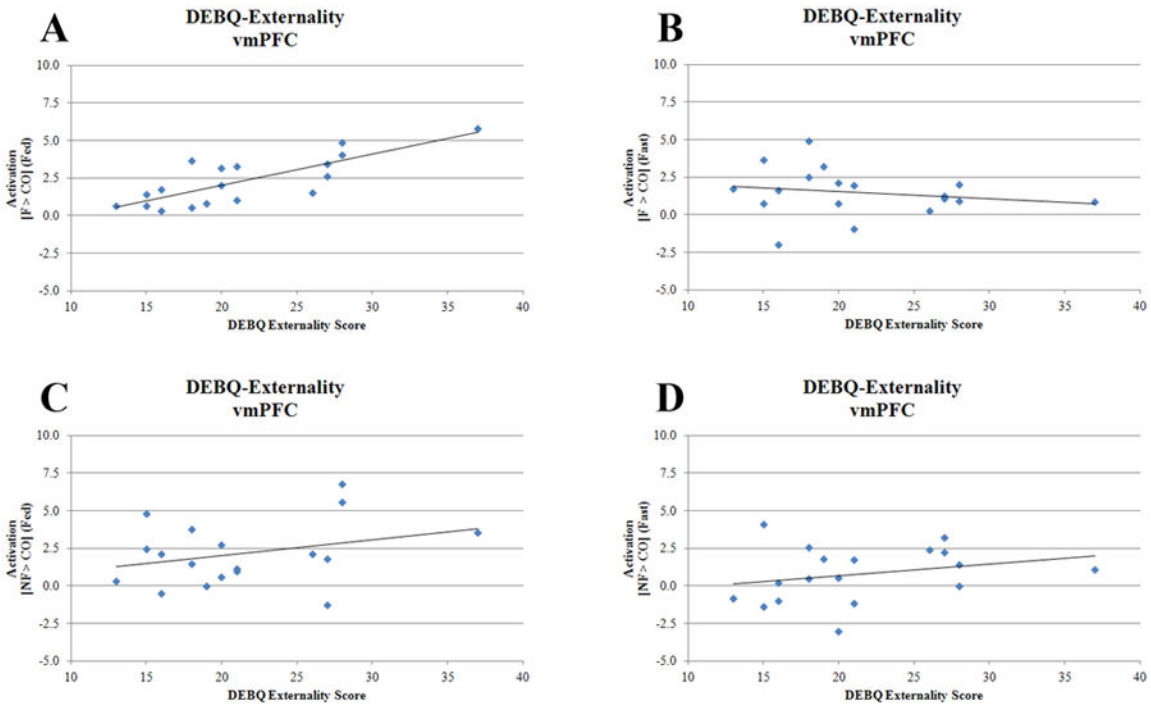

Figure 4.

A) Illustrative plot of correlation between Externality and [F > CO] response, as extracted from the cluster of significant, positive correlation (threshold, $p < 0.001$) under the Fed session. However, non-significant relationships between Externality scores were observed with **B)** [F > CO] response under the Fast session, **C)** [NF > CO] response under the Fed session and **D)** [NF > CO] response under the Fast session.

Table 1

	Lean, BMI ≤ 27 (n = 11)			Obese, BMI ≥ 30 (n = 7)		
	Mean	**(SD)**	**n (%)**	**Mean**	**(SD)**	**n (%)**
Age	23.50	(4.39)		30.14	(4.98)	
Caucasian			10 (91%)			6 (86%)
Education (yrs.)	16.00	(1.18)		15.86	(2.27)	
Height (cm)	165.75	(8.07)		165.56	(6.60)	
Weight (kg)	61.90	(7.84)		98.37	(11.18)	
BMI (kg/m^2)	22.19	(2.09)		36.34	(4.16)	

Chemosens Percept. Author manuscript; available in PMC 2014 December 04.

Table 2

	Cluster - Level		Voxel - Level (peak)		Peak MNI coordinates (mm)		
	Cluster Size (k_E)	***q* (FWE)[b]**	***q* (FWE)**	**Z_E**	**x**	**y**	**z**
[a]Food Odors > Control *[F > CO]*							
Medial Prefrontal Cortex and Anterior Cingulate, extending to Left Inferior Frontal Gyrus (pars orbitalis) with subpeak (-40, 32, -14)	4759	< 0.001	< 0.001	5.92	-2	34	-12
Left Amygdala, Piriform Cortex, Hippocampus, extending to Precuneus with subpeak (-4, -62, 14)	3772	< 0.001	< 0.001	6.29	-26	-18	-16
Right Amygdala, Piriform Cortex, Hippocampus	488	< 0.001	0.001	5.72	26	0	-20
[a]Non-Food Odors > Control *[NF > CO]*							
Precuneus	1441	< 0.001	0.058	4.81	0	-62	18
Left Amygdala, Piriform Cortex, Hippocampus	1267	< 0.001	< 0.001	6.25	-20	-2	-22
Right Amygdala, Piriform Cortex, Hippocampus	505	< 0.001	0.037	5.85	24	0	-22
Medial Prefrontal Cortex	441	< 0.001	0.089	4.71	2	50	-16
Left Inferior Frontal Gyrus (pars orbitalis)	287	< 0.001	0.01	5.22	-38	32	-16
Medial Prefrontal Cortex	244	< 0.001	0.351	4.32	-14	60	-12

[a]Main effect collapsed across session.

[b]Significance was assessed at a cluster level, whole-brain volume corrected using the familywise error, q(FWE)<0.005 with a voxel-wise height threshold of p<0.001.